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Award Number: W81XWH-14-2-0153

TITLE: Decreasing Skin Graft Contraction through Topical Wound Bed Preparation with Anti-Inflammatory Agents

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CONTRACTING ORGANIZATION: The Geneva Foundation
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14. ABSTRACT
The objectives of this proposal are to identify the dose and application schedule of a specific topical anti-inflammatory drug that will both reduce and shorten the inflammatory state of the recipient wound bed and thus decrease skin graft contraction.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Introduction:

We hypothesize that the elevated and prolonged inflammatory state of the recipient wound bed is a causative factor in the development of skin graft contraction. Using a porcine model of skin graft contraction, we will screen for anti-inflammatory agents (dose, schedule of administration, drug class) that reduce inflammatory cytokines in the recipient wound bed during 6 days post-wounding. We will then validate the effectiveness of the anti-inflammatory agent, dose and schedule to reduce contraction of the grafted split-thickness skin by allowing the experimental animal to survive for a longer period of time. Specifically, the aims of the proposal are to develop treatments that modulate inflammation and decrease skin graft contraction. We will achieve this by (1) identifying a dose and schedule of anti-inflammatory drug that most effectively blocks excessive inflammation of the recipient wound bed as defined by inflammatory markers and (2) validate the schedule and dose of anti-inflammatory drug shown to reduce inflammation of the recipient wound bed to decrease skin graft contraction.

Keywords:

-Inflammation
-Anti-inflammatory agents
-Wound healing
-Contraction

ACCOMPLISHMENTS:

What were the major goals of the project?

Develop treatments that modulate inflammation and decrease skin graft contraction

A.1.2.1 Identify a dose and schedule of anti-inflammatory drug that most effectively blocks excessive inflammation of the recipient wound bed as defined by inflammatory markers.

A.1.2.2 Validate the schedule and dose of anti-inflammatory drug shown to reduce inflammation of the recipient wound bed to decrease skin graft contraction. This will be performed on a larger wound model.

What was accomplished under these goals?

A.1.2.1: Under this goal we found that application of the anti-inflammatory drug prior to grafting at the dosages proposed led to a high incidence of graft failure with decreases in inflammatory markers. It appears that inflammatory modulation prior to grafting is difficult to control. Therefore, we have modified the treatment plan and have applied the treatment over the graft, either at the time of grafting or several days later. To date, we have treated two animals and graft take has improved when compared to the prior experiment. Further results are pending.

A.1.2.2: We are currently still making progress on A.1.2.1 and therefore nothing we have not started any validation experiments where larger wounds are used. However, we have developed the larger wound model and have had success with its use in other experiments and will be ready once A.1.2.1. results are final. A NCE was submitted several weeks ago to allow extension of this work into FY17.

What opportunities for training and professional development has the project provided?

This project has provided research training for post-doctoral fellows with study design and execution including harvesting skin grafts, applying split-thickness skin grafts to wounds and suturing grafts in place. The preliminary findings have been presented at local conferences but there has been no publications to date.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

A.1.2.1: We are currently scheduled to perform the late treatment procedures (2 swine) on 23 and 26Sept. These swine will be sacrificed at 28 days post-treatment. Once the late treatment group data has been analyzed we plan to perform an additional procedure with treatment on Day 0 and again on Day 3.

A.1.2.2: Once A.1.2.1 is complete, will begin the validation phase utilizing the larger wound model. We expect to start this by the next report date.

Impact

What was the impact on the development of the principal discipline(s) of the project?

In this project we have learned that placement of anti-inflammatory modulators prior to a split-thickness skin graft inevitably leads to graft failure. This is likely due to the inhibition of angiogenesis and migration of essential nutrients to the graft.

What was the impact on other disciplines?

It is known that imbibition is vital for skin graft survival. Based on our results, we have demonstrated that application of a substance that limits imbibition has a profound effect on graft survival. This knowledge will likely prevent other scientists and clinicians from placing materials between a wound and skin graft and compromising the integrity or "take" of their graft.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

Changes/Problems

Changes in approach and reasons for change

Old Approach: Placement of anti-inflammatory agent over wound bed followed by placement of skin graft. This led to graft failure.

New Approach: Placement of skin graft prior to applying anti-inflammatory agents. This is not a significant change and was discussed in the proposal.

Actual or anticipated problems or delays and actions or plans to resolve them

Potential Problem: Failure of grafts to take despite new approach. We have completed 2 "early" treatment animals and there was 100% graft take based on visual appearance. Histology is pending.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

No changes.

PRODUCTS:

Nothing to report.

Publications, conference papers, and presentations

Nothing to report.

Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Rodney Chan, MD.
Project Role:	Principal Investigator
Nearest person month worked:	6 (Calendar)
Contribution to Project:	Dr. Chan is the PI of the award.

Name:	Kai Leung, PhD.
Project Role:	Co-Principal Investigator
Nearest person month worked:	1
Contribution to Project:	Dr. Leung is the Co-PI of the award.

Name:	John Fletcher, M.D.
Project Role:	Surgical Resident
Nearest person month worked:	3
Contribution to Project:	Dr. Fletcher is the Surgical Resident of this award.

Name:	Chris Corkins, M.D.
Project Role:	Surgical Resident
Nearest person month worked:	3
Contribution to Project:	Dr. Corkins is a Surgical Resident assisting with this project.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

Special Reporting Requirements

Quad Chart: The Quad Chart (available on https://www.usamraa.army.mil) shall be updated and submitted as an appendix.

Appendices

None

Decreasing skin graft contraction through topical wound bed preparation with anti-inflammatory agents

W81XWH-14-2-0153

PI: Rodney Chan MD/Kai Leung PhD **Org:** USAISR/The Geneva Foundation **Award Amount:** $881,310

Study/Product Aim(s)

1. Identify a dose and schedule of anti-inflammatory drug that most effectively blocks excessive inflammation of the recipient wound bed as defined by inflammatory markers.
2. Validate the dose and schedule of anti-inflammatory drug shown to reduce inflammation of the recipient wound bed to decrease skin graft contraction.

Approach

A porcine model of excisional wound was developed to study wound inflammation and its effect on skin graft contraction. Wound bed modulation using anti-inflammatory treatments are first applied to a screening model and then validated on an experimental model with larger wounds to study skin graft contraction.

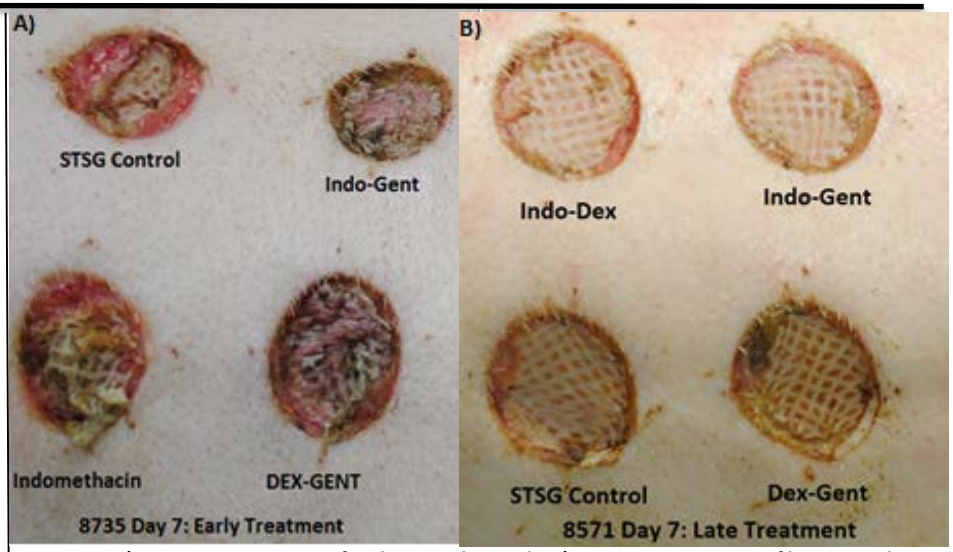

Figure 1: A) Day 7 representation of early treated wounds. B) Day 7 representation of late treated wounds.

Timeline and Cost

Activities CY	14	15	16	17
Aim 1 (Identify drug/schedule/dose) using screening model				
Aim 2 (Identify drug/schedule/dose) using validation model				
Estimated Budget ($881.3k)	**$000**	**$434**	**$447**	**$000**

Updated: 12 October 2016

Goals/Milestones

CY15 Goal – Screening of anti-inflammatory therapies

- ☑ IRB Approval of both screening and validation porcine wound bed preparation model
- ☑ Establishment of Screening model to examine the effect of topical anti-inflammatory drugs
- ☑ Establishment of Validation model to examine the effect of topical anti-inflammatory drugs
- ☑ Establish dose and schedule of anti-inflammatory drug to best decrease inflammatory markers
- ☑ Establish wound model for large wound validation

CY16 Goals – Start validation model of anti-inflammatory therapies

- ☑ Establish dose and schedule of anti-inflammatory drug to best decrease inflammatory markers with use of the screening model
- ❑ Validate the optimal dose and schedule of anti-inflammatory drug to decrease skin graft contraction on large wounds (model developed; first treatment Nov2016)

CY17 Goals – Complete large wound validation model

- ❑ Continue validation phase with the optimal dose and schedule of anti-inflammatory drug to decrease skin graft contraction on large wounds (first treatment Nov2016)
- ❑ Complete data collection and analysis

Comments/Challenges/Issues/Concerns: Prior attempt at placing skin graft over treatment medium led to graft failure. New method of placing the hydrogel treatment over the STSG has been successful to date. Current progress limited by availability of vivarium and operating room times.

Budget Expenditure as of 9.30.16

Projected Expenditure: $ 881,310

Actual Expenditure: $437,929